REMARKS

Claims 9-11 are in this application. Claims 5-8 are being cancelled in this response. Claims 1-4 were cancelled in the Response to the Official Action of April 12, 2002. Applicants preserve all rights to file one or more continuation and/or divisional applications for subject matter disclosed and not claimed in this application. The Annexes were supplied previously. If the Examiner requires additional copies of annexes, please contact the undersigned.

The Examiner has rejected claims 9-11 as being obvious under 35 USC 103(a) over the combination of D'Amato, Masiero et al. and Patierno et al. Applicants respectfully traverse this rejection.

The method of Claim 9 of the subject application is characterized **by the use of thalidomide in the treatment of hepatocellular carcinoma**. None of the cited references teaches or suggests the use of thalidomide in the treatment of hepatocellular carcinoma or the effects associated with this cancer.

U.S. Patent No. 5,696,092 describes the methods and compositions that prevent or inhibit metastases of cancers of epithelial cell origin, especially human prostate cancer. The Masiero, et al reference discloses that thalidomide was shown to inhibit growth factor induced neo-vessel formation and is in Phase II clinical trials for prostate cancer, glioblastoma multiforme and breast cancer. US Patent No. 5,629,327 relates to the methods and composition for preventing unwanted angiogenesis in a human or animal by administering compounds such as thalidomide and related compounds. However, none of the three citations teaches or suggests the use of thalidomide in the treatment hepatocellular carcinoma.

It is known that many cancers are involved with angiogenesis and derived from epithelial cells. For instance, as mentioned in Tables 3 to 8 of Steven Brem, "Angiogenesis and Cancer Control: From Concept to Therapeutic Trial," (see Annex 1), angiogenesis is a phenomenon related to many cancers, including breast, lung (non-small cell), pancreas, malignant glioma, ovary, prostate, colon, acute leukemias, solid tumors, colorectal, renal, Kaposi's sarcoma, von Hippel-Lindau, leiomyosarcoma, brain, melanoma, and gastrointestinal cancers. Also as mentioned on the website, Department of Human Biological Chemistry & Genetics at The University of Texas Medical Branch at Galveston (see Annex 2), colon cancer can result from progressive loss of regulation of the normal growth inhibitory, differentiation and apoptotic signals in colonic epithelial cells; and on the website, The Ovarian Cancer Forum of Med Help International (see Annex 3), the most common type of ovarian cancer is epithelial cancer - this type of cancer arises from the cells covering the surface of the ovary.

On the other hand, liver related cancers are mainly divided into two types: one is derived from hepatocytes and the other is metastasized from other tissues or organs. The former one is the so-called primary malignant hepatic tumors. Among others, hepatocellular carcinoma (hepatoma) is well known. In addition, liver related cancers also include the cancers derived from the tissues and cells in liver, such as

hemangiosarcoma derived from blood vessels, hepatoblastoma derived from hepatogenic cells, and cholangiocarcinoma derived from the bile duct.

Given the above, it is understood that the mechanisms of the formation of cancers, including liver related cancers, are quite diverse.

So thus far, it appears that no medicine is expected to be effective in treating all types of cancers. For instance, Navelbine® (see Annex 4), has received an approval in two specific cancers, i.e., non-small lung cancer and breast cancer (which is a type of epithelial cell associated cancer). However, Navelbine® is **not** effective in combating all types of cancers, particularly hepatocellular carcinoma. Instead, Navelbine® has adverse effects on hepatic organ sites. Furthermore, doxorubicin is helpful for treating brain cancers, which is recognized as an angiogenic cancer as mentioned above. Furthermore, as reported in the results of the delivery of doxorubicin (Adriamycin) to the brain for treatment of tumors (see Annex 5), and the study on brain tumour drug delivery (see Annex 6), doxorubicin is an effective chemotherapeutic drug for breast cancer and since 17% of all breast cancer patients experience metastases to the brain, doxorubicin could be potentially useful in the treatment of these tumors. However, a patient suffered from brain tumors while having developed liver disease, could not take an effective dose to treat the former cancer, simply because of undesirable side effects (see Annex 7). The above two examples clearly elucidate that anti-cancer drugs are effective in some specific cancers only, but not effective in other types of cancers, particularly hepatocellular carcinoma.

Given the above, without undergoing experimentation or clinical trials, there is no way to expect that a drug, which can treat cancers of epithelia cell origin or associated with angiogenesis, can specifically treat hepatocellular carcinoma. Applicants believe that without the teachings of the subject invention and the evidence provided in the subject invention, skilled artisans would by no means infer from the three cited references that thalidomide can specifically treat hepatocellular carcinoma. The use of thalidomide to treat hepatocellular carcinoma is not obvious from the combination of the cited references as none of the references disclose or suggest either alone or in combination that thalidomide can be used to treat this specific type of cancer.

Therefore, it is respectfully requested that the rejection be withdrawn.

Accordingly, applicants submit that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

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